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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 10-61
Rockville, Maryland 20852

RE: Draft Guidance for Industry on Clinical Investigator Financial Disclosure: Docket No. 99D-4396; 64 Fed.Reg. 57640 (October 26, 1999)

Dear Sir/Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, happier, healthier and more productive lives. Investing over $24 billion annually in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures. PhRMA is pleased to submit these comments on PhRMA's draft guidance on financial disclosure for clinical investigators.

Definition of Covered Clinical Study

The guidance document describes, virtually verbatim, the definition of a covered clinical study contained in 2 1 CFR 54.2(e). However, the guidance document does not provide further insight or interpretation regarding the types of studies that are covered. The guidance states that phase 1 tolerance studies and pharmacokinetic studies, and most clinical pharmacology studies (unless they are critical to an efficacy determination) are generally not included under the definition. This wording is ambiguous with respect to certain types of studies. For example, there are a number of special pharmacokinetic studies that are commonly conducted during drug development. These include pharmacokinetic studies in special sub-populations (age/gender, renal-impaired, hepatic- impaired) and drug interaction studies. Such studies may be considered phase 1 studies by their nature, but are often conducted during phase 2 or 3 drug development.

The primary purpose of such studies is to determine whether the pharmacokinetics of the drug are different in certain sub-populations, or changed by co-administration with other drugs (or affect the pharmacokinetics of the other drugs). The results may or may not lead to modified dosing recommendations for certain sub-populations. However, such studies are generally not critical to the overall efficacy determination, nor do they make a significant contribution to the overall demonstration of safety. Therefore, for the sake of clarity this section of the guidance should be modified to explicitly state that pharmacokinetic studies in special populations (e.g., elderly, renal-impaired, hepatic-impaired) and drug interaction studies are generally not covered by the rule.

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Question No. 5 -- Definition of Sponsor

A. Consistent Definition

The definition of "sponsor" has a well-established definition in clinical investigation. This definition is guided by which party holds the IND (where applicable), as well as by the definition of "sponsor" in 2 1 CFR part 3 12 (i.e., the party "who takes responsibility for and initiates the clinical investigation"). The Guidance should recognize this established definition and clarify that the term "sponsor" has the same meaning as in the IND regulations. To adopt a different and unique definition of this term in the Financial Disclosure regulations would lead to confusion and inconsistencies. Utilizing the definition from the IND regulations also will resolve the uncertainty regarding the example of a party whose only involvement in a trial is to supply drug - it is clear under the IND regulations that this fact alone would not necessarily make that party a "sponsor." Using that example, the question of sponsorship typically would be designated in a written contract, whereby one of the parties, in the language of the IND regulations, agrees to "take responsibility for and initiate the clinical investigation."

B. Publicly-Sponsored Studies

Publicly-sponsored studies should, in FDA's enforcement and interpretive discretion, be treated as outside the definition of "covered clinical studies"

As currently interpreted in the draft guidance, the financial disclosure regulations would operate to impose inappropriate compliance burdens on governmental agencies that sponsor important clinical research, and/or on pharmaceutical companies that may lend modest support to such research, such as in-kind donation of study drug(s). As matters stand, these burdens would be triggered whenever a publicly-sponsored study that meets the criteria for being "covered" (see 21 C.F.R. § 54.2(e)) is submitted to FDA in support of a marketing application (e.g., an sNDA seeking labeling changes). As explained below, these burdens simply cannot be justified in the distinctive context of publicly-sponsored research, where there is no meaningful potential for the kind of economically-motivated bias that the regulations seek to address.

Several governmental agencies, including most notably many components of the National Institutes of Health, have compiled a distinguished record of sponsoring vital clinical research directed at the prevention, diagnosis, and treatment of conditions such as HIV-infection, cancer, and others with major public health impact. This publicly-funded research has played an important role in defining public health policy and in the development of model treatment practices that guide practitioners in the selection of treatment regimens. Some of this valuable research is conducted through networks of clinical trial sites that are organized and/or supported by the sponsoring governmental agencies.

It is not uncommon for private pharmaceutical firms to lend modest support to the clinical research that governmental agencies sponsor; the nature of this limited support is described below. However, private firms do not set the research agenda that public agencies pursue, do not typically originate protocols (although an opportunity to comment in the design phase may be available), and rarely if ever participate in the management of publicly-sponsored studies. In therapeutic areas characterized by multiple-agent treatment regimens, such as HIV-infection, protocols sponsored by governmental agencies will typically encompass drug products marketed by two or more different pharmaceutical firms. It is the governmental agency, and not any of the private companies, that exercises complete control over communication with, and selection, training, monitoring, and compensation of, participating clinical investigators. Moreover, the public agency, as the IND-holder, must fulfill all of the regulatory obligations of the sponsor. As well, the governmental agency takes full responsibility for analyzing study data and preparing final study reports: while pharmaceutical firms may be privileged to review drafts, the public sponsor retains ultimate and complete control.

Financial support from private interests is generally limited to provision of study drug, and/or relatively modest monetary contributions. At times, for instance, pharmaceutical firms whose drugs are being studied in a publicly-sponsored protocol may be asked to make "fair share" contributions to support laboratory work beyond the government-funded, in-house capabilities of the study sites. Any such contributions are remitted directly to the governmental agency, which manages study expenses, vis-à-vis clinical sites, in its sole discretion as study sponsor and administrator.

According to the draft guidance, see question and answer # 5, both governmental sponsors and pharmaceutical firms that lend modest support (often limited to provision of study drug(s)) would qualify as a "sponsor" for purposes of financial disclosure. Assuming that a given publicly-conducted study is ultimately submitted in support of a marketing application and otherwise qualifies as "covered," multiple compliance obligations arise: specifically, the need to capture financial arrangements between investigators and, not only the sponsoring governmental agency, but also all private firm(s) that lend subsidiary support. Moreover, given uncertainty at the threshold as to whether a publicly-sponsored study may ultimately be submitted in support of a marketing application, there may be no choice but to err on the side of caution and initiate financial disclosure compliance processes at the start of each study. See question and answer 9, regarding the need to collect financial disclosure information prior to study start. Often, these efforts will prove to have been unnecessary, if no private firm ultimately makes use of the data for regulatory purposes.

The resultant wide-ranging compliance burdens are misplaced and not justified in the distinctive context of publicly-sponsored research. A sponsoring governmental agency does not stand to benefit financially if the data generated in a "covered" study it sponsors should prove valuable in demonstrating the effectiveness of a marketed product. Such agencies do not take royalties or other compensation from pharmaceutical companies who make use of data generated in their studies, nor do the agencies commercialize or license products in their

own right. Pharmaceutical firms that lend modest support to publicly-sponsored studies do, obviously, have prospective commercial interests, but their lack of operational control (in such respects as selecting, monitoring, and communicating with investigators), and their lack of visibility to investigators, renders those interests of little or no significance for purposes of financial disclosure.

The fundamental premise of the financial disclosure regulations is that the *shared* commercial interests of study sponsors and clinical investigators, as captured by the defined four categories of potentially disclosable interests, can be a source of conscious or inadvertent bias. In the context of publicly-supported research, however, this premise has no meaningful application, as explained further below with reference to the four defined categories. *Because both governmental agencies and pharmaceutical firms could be considered study "sponsors" for purposes of financial disclosure, it would be* ***multiple*** *sets of arrangements with investigators, rather than those of just the ultimate marketing application sponsor, that are called into question:*

- **Compensation potentially affected by the outcome of the covered study [21 C.F.R. §§ 54.4(a)(3)(i), 54.2(a)] :**

  Governmental sponsors have neither the need (given the prestige of participating in publicly-funded research) nor the resources to compensate investigators in such a manner that the total amount could vary with outcome. Moreover, given that governmental bodies have no commercial interest in the product(s) under study, they would in any event have no reason to attempt to favor one outcome over another.

  Private pharmaceutical firms that lend modest support neither negotiate nor pay compensation to investigators participating in publicly-sponsored studies.

- **Significant payments of other sorts from the sponsor of the covered study [21 C.F.R. §§ 54.4(a)(3)(ii), 54.2(f)]:**

  Again, limited resources severely constrain the ability of public bodies to compensate clinical investigators for speaking or consulting. Moreover, in the completely unlikely event any investigator was fortunate enough to receive supplementary income from a governmental sponsor, he/she could not reasonably be expected to be influenced by this source of income, because he/she could not possibly conceive of a study outcome that might be favored by a public sponsor with no commercial interest.

  Private pharmaceutical firms that lend modest support might have the resources to compensate participating clinical investigators for speaking, consulting, and the like, but again, this is of little or no significance in the context of publicly-sponsored studies. Operationally, private firms simply do not have a presence in publicly-sponsored studies from the standpoint of investigators: selection and monitoring of, and communication with, investigators is carried out by the governmental sponsor. As a practical matter, this

lack of private firm visibility effectively negates the potential for intentional or inadvertent influence peddling (through "payments of other sorts" or otherwise). Moreover, with the possible presence of multiple private firms that qualify as "sponsor" for purposes of financial disclosure, the potential for bias to enter in favor of any one such firm is further reduced. Finally, a marketing application sponsor can not reasonably be expected to monitor and report on investigators' receipts of "payments of other sorts" from other private firms. Administering this category is thus unworkable.

- **Proprietary interest in the tested product [21 C.F.R. §§ 54.4(a)(3)(iii), 54.2(c)]:**

  Although participating investigators might hold such interests, in the context of publicly-sponsored studies, the likelihood is of multiple products being under investigation. The prospect of bias entering in favor of any one of them is thus remote. Moreover, as noted above, a marketing application sponsor can not reasonably be expected to monitor investigators' "proprietary interests" in test products sponsored by other private firms. Administering this category is thus unworkable.

- **Significant equity interest in the sponsor of the covered study [21 C.F.R. §§ 54.4(a)(3)(iv), 54.2(b)]:**

  It is impossible to hold an equity interest in governmental sponsors of publicly-funded studies, inasmuch as they are agencies of the United States Department of Health and Human Services.

  While investigators might conceivably hold stock in one or more private firms that lend modest support to publicly-sponsored studies, again, as practical matter, any such interests are simply too remote from the standpoint of potential bias. The lack of private firm visibility in the administration of publicly-sponsored studies effectively negates the potential that investigators will be swayed by consciousness of their equity holdings. Moreover, as noted above, with the possible presence of multiple private firms qualifying as "sponsor," the potential for bias to enter in favor of any one such firm is further reduced. Lastly, and again as already noted, a marketing application sponsor can not reasonably be expected to monitor and report on investigators' interests (in this case, equity holdings) in other private firms.

In the preamble appearing in the *Federal Register* on December 3 1, 1998, FDA recounted what amounts to its summary rejection of a plea (from two clinical investigators at an unnamed government agency) that publicly-sponsored research be exempted from the financial disclosure requirements. PhRMA respectfully suggests that it is time to revisit this summary disposition, in light of experience gained with the financial disclosure regulations and a fuller understanding of their costs and benefits. As discussed above, the regulations as written are ill-fitted to publicly-sponsored research, and the policy purposes of the regulations are not well-served by requiring public agencies that sponsor clinical research, and/or private firms that lend modest support, to report, potentially on multiple sets of

financial arrangements. Yet that is the effect of the regulations as currently written and interpreted in the draft guidance. FDA should reverse course, and explicitly provide in the guidance that publicly-sponsored research is deemed, in FDA's enforcement and interpretative discretion, to be outside the definition of "covered clinical study."

Question No. 9 - Requiring Collection of Information Prior to Study Start

21 CFR § 312.53(c)(4) requires that, prior to study start, the sponsor must collect "sufficient accurate financial information to allow the sponsor to submit complete and accurate disclosure statements" under the Financial Disclosure regulations. "Financial information" could include information on proprietary interests, compensation based on outcome, payments or stock. In order to avoid significant and unnecessary delays to study start-ups, **it is critical that the Guidance clarify that it is in the sponsor's judgment to determine what types of financial information are "sufficient" to enable complete and accurate disclosure in a marketing application.** For example, a sponsor should not be required to collect certain types of financial information if it has decided that it will not use that particular information to meet reporting obligations or make decisions regarding investigator bias. The Guidance should also clarify that, while the sponsor should evaluate necessary financial information so that it is aware of potential bias before the study starts, it is in the sponsor's discretion to determine whether the information deemed necessary for this purpose should be obtained from the investigator or internally.

Question No. 10 – Definition of "Investigator"

A. Clarification Needed

The Guidance clarifies that an "investigator or subinvestigator" is an individual

- Who takes responsibility for the investigation;
- Under whose immediate direction and control the drug/biologic is administered; and
- Who is directly involved in the treatment and evaluation of research subjects.

These criteria are appropriately based on the definition of the same term in the IND regulations. However, there are three clarifications needed based on this definition. First, the Guidance should clarify that the above definition is controlling and should not refer to individuals listed on item 6 of the Form FDA 1572, due to the different (and sometimes variable) standards used to determine inclusion on that form. Second, the Guidance should be explicit that the above criteria refer primarily to physician investigators (i.e., directing administration of drug and generally responsible for the investigation). Finally, the final paragraph in this section of the Guidance excludes individuals who "do not make direct and significant contributions to the data." This phrase should not be used because it introduces anew standard or criteria (i.e., whether or not an individual makes a direct and significant contribution to the data) which is not part of the definition. Use of this phrase in the Guidance document, even in the negative, will leave sponsors wondering whether to include

an individual (e.g., a rater or EKG reader) who clearly does not meet the criteria for an "investigator" but may perhaps make a "direct and significant contribution to the data."

B. Discussion at November 1, 1999 DIA Workshop

As was pointed out at the November 1, 1999 DIA workshop on the Financial Disclosure guidance document, it is common practice at many study sites to list all individuals involved with the conduct of the study on the Form FDA 1572, including support staff who are not directly involved in the treatment or evaluation of patients. If financial disclosure were to be required for all such individuals, there would be a significant amount of unnecessary data collection and reporting.

The FDA representatives at the November 1 workshop recognized this point, and clarified that the guidance's reference to individuals listed on the Form 1572 was an example, not the final determinant of whether financial disclosure is required. FDA staff further clarified that, unless such individuals otherwise meet the definition of clinical investigator, hospital support staff who do not make a direct and significant contribution to the data are not covered by the rule.

In order to avoid misinterpretation of the scope of the rule, and as pointed out above, the clarification provided at the DIA workshop should be made explicit in the Guidance document.

Question No. 12 – Meaning of "Completion of Study"

The draft guidance states that "completion of the study means that all study subjects have been enrolled and follow up of primary endpoint data on all subjects has been completed in accordance with the clinical protocol." In most multi-center studies, however, timing for completion of enrollment and follow up of primary endpoint data vary widely from one site to the next. It is not unusual for one site to complete its participation in the study many months apart from other sites, and it would be difficult if not totally impractical, for any particular investigator to know when all other investigators have completed the study. Therefore, a site-specific approach would be more practical, and would result in clearer understanding of when the reporting period ends.

Accordingly, PhRMA recommends that the answer to item 12 (p.8) be clarified to read "Completion of the study for an individual investigator means that all study subjects have been enrolled and follow up of primary endpoint data has been completed on all subjects enrolled at the investigator's study site in accordance with the study protocol. Alternatively, a sponsor may choose to define completion of the study based on when follow up of primary endpoint data has been completed at all sites in accordance with the protocol. Sponsors are encouraged to utilize a consistent approach for all studies submitted in an application."

Question 28 – Payments of other sorts

In response to question 28, the guidance provides examples of documentation that applicants should retain to support their filings. The language of the guidance would be clearer, however, if it explicitly indicated that the examples are of documents that would be supplied to the applicant by the investigator. Thus, PhRMA recommends that the second sentence in the answer be modified by the addition of the underlined words:

> "for example, detail provided by investigators, check stubs" and "personal equity holdings and payments of other sorts"

The draft guidance, although not absolutely clear, implies that sponsors can rely on information provided by investigators. Since publication of the draft guidance, FDA representatives have indicated that it would be reasonable to rely solely on information provided by investigators, provided the sponsor deems the information to be reliable.

Payments of other sorts are payments that benefit or enrich the investigator, such as honoraria or research grants. As such, the category should not include reimbursement for out-of-pocket expenses; for example, cab fare to an in-town meeting or a plane ticket to a meeting at which an investigator is speaking. Including reimbursements for out-of-pocket expenses is inconsistent with the underlying purpose of the rule, distorts the information received from investigators, and imposes additional record keeping requirements on investigators. PhRMA urges FDA to reconsider, and change, this interpretation of the requirements.

Equity Interest in Sponsor or Parent Company

The rule requires applicants to certify that investigators do not have an equity interest in, or provide information about an investigator's equity interest in, the sponsor of the clinical trial. In many instances, the sponsor of a specific clinical trial is a not-publicly traded subsidiary of a parent corporation that is publicly-traded. In such instances, it is not possible for an investigator to hold an equity interest in the subsidiary that is the sponsor of the trial, but the investigator's relationship, for purposes of the trial, is with the subsidiary, not the parent corporation.

Industry understands that when the sponsor of a trial is a not publicly-traded subsidiary of a publicly-traded parent corporation, the sponsor does not have to collect information about, or certify concerning an investigator's equity holdings in, a parent corporation, Indeed, the FDA representative at the November DIA workshop confirmed that interpretation of the rule. Any other interpretation of the rule would impose complex reporting requirements on investigators and sponsors, to track the relationships between companies, that would distract from the investigator's attention to the protocol requirements for the study.

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In summary, PhRMA recommends that FDA clarify some aspects of the answers to the questions posed in the Guidance. We would be pleased to discuss these comments with you if that would be helpful.

Sincerely,

Marjorie E. Powell